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AN INVESTIGATION OF CHANGES IN THE BLOOD AND URINE RESULTING FROM FATIGUE.

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The chemistry of fatigue has attracted the attention of investigators from the time of Du Bois-Reymond who in 1859 reported experiments which showed that a tetanized frog's muscle was more acid than an untetanized one. It had previously been demonstrated that the acidity arising in excised muscles was probably due to lactic acid. Ranke who attempted to identify and study quantitatively the products of muscular contraction, concluded that fatigue resulted from the presence of certain metabolic products and that the activity of the muscle might be restored by the removal of these metabolites by the blood. As individuals of this class of fatigue substances, he named carbon dioxide, potassium acid phosphate, and lactic acid. Lee found evidence that among the products of metabolism in pathological conditions, β-oxybutyric acid, indol, skatol, and methyl mercaptan had a fatiguing action similar to the above-named substances.

When evidence pointed to the presence of certain substances after fatigue, attention turned to the mechanism of their removal. Much time has been devoted to the investigation of the relation of respiration to fatigue. Geppert and Zuntz concluded that the acceleration of respiration observed during exercise might be attributed to substances which, arising in muscular work, entered into the blood and directly stimulated the respiratory center. Loewy found that if the tissues were supplied with sufficient oxygen during muscular work, the respiratory quotient remained unchanged. Higley and Bowen, in a series of carefully controlled experiments, found that the rate of production of carbon dioxide remained constant for constant work.

Little is to be found in the literature regarding perspiration and muscular fatigue. Viale observed that the concentration of sodium chloride increased during a march. Kittsteiner stated that muscular activity had no direct influence on the acidity of perspiration. Talbert in a preliminary report noted that the hydrogen-ion concentration of perspiration was increased during exercise.

Since Scott has adequately summarized our present knowledge of changes in individual urinary constituents resulting from fatigue, we shall refer only to those observations which have been made on the titratable acidity of the urine. Klupfel reported a few experiments on men from which he concluded that the daily acid content of urine was greater on a day of work than on a day of rest. Sawicki, after performing similar experiments, gave it as his opinion that "the quantity of acid secreted by the urine depends more on the quality and quantity of the food ingested than on rest and work." Aducco later published results which showed that in the course of fatigue, the urine of dogs became alkaline, due to the presence of alkali carbonates. Benedicenti, in confirmation of Klupfel's observations, found that the urine of marching soldiers was always abnormally acid after a prolonged march.

The attention of the writer has been centered on the hydrogen-ion concentration of the urine and blood plasma, and the alkaline reserve of the latter, as modified by muscular work. The conception of the alkaline reserve of the blood has been clearly defined by Van Slyke and collaborators in connection with their studies of acidosis. The depletion of this reserve alkali might indicate either the presence of acids in abnormal quantities in the organism, or an impaired mechanism for the elimination of the acids produced. Henderson and Haggard have differentiated between a condition of true acidosis and the temporary lowering of the reserve alkali by overbreathing.

That the blood maintains a constant reaction with great persistency, in spite of marked changes in its alkaline reserve, is well known. This constancy, however, may be apparent rather than real. Hasselbalch and Lundsgaard, in their accurate investigation of the reaction of blood at body temperature, found that, with sufficiently delicate methods of determination, changes in the hydrogen-ion concentration of the blood, correlated with changes in CO_2 tension within physiological limits, might be detected. Milroy observed a fall in the hydrogen-ion concentration of the blood resulting from pulmonary ventilation. Henderson (1909) has shown that the equation $C_H = K \frac{H_2CO_3}{\gamma NaHCO_3}$ closely expresses the relationship between the hydrogen-ion concentration (C_H), the carbon dioxide tension, and the bicarbonate content or alkaline reserve of the blood. It is seen, therefore, that any change in the concentration of either of the variables on the right-hand side of the equation would result in a corresponding change in the other variable in order that the constancy of the reaction of the blood might be preserved.

In contrast with the behavior of the blood, the urine shows comparatively wide variations in its reaction. Henderson (1911) has shown that the normal reaction of the urine varies within the limits of a solution containing mono- and di-sodium phosphate in the approximate ratio of 9 to 1 on the acid side and of 1 to 9 on the alkaline side, corresponding to the hydrogen-ion concentrations of 20×10^{-7} and 0.2×10^{-7} respectively. The character of the diet is one of the most potent of the many factors influencing the urinary reaction. Our data may be of value in indicating the extent to which fatigue may be regarded as one of these factors.

The studies here to be reported were made for the most part on the urine of men and the blood of dogs. In a limited number of cases, data were obtained on both the urine and blood of the same subjects.

In preliminary experiments, fatigue was induced in the animals by causing them to run in a revolving wheel, such as Mosso employed. Later, a motor-driven treadmill, the speed of which could be varied up to 10 miles per hour, provided a more suitable means of fatiguing the subjects. Data on the reaction of the urine of men at rest were obtained from men convalescing from minor surgical operations. The histories and diets of these men were carefully followed. To obtain our figures on fatigued subjects, we determined the reaction of the urine of men engaged in mechanical operations of various degrees of arduousness at an automobile factory, of men participating in a 12-mile Marathon race, of entrants in a 6-day bicycle race, and of a man on a 10-mile walk. In the case of the latter subject the blood also was studied. Urine specimens were collected at comparable times in each series of experiments.

Blood was drawn from the external jugular vein of the dogs, collected under paraffin oil without exposure to air, oxalated and centrifugated according to the procedure described by Van Slyke. The reaction of the plasma was determined electrometrically with a Clark electrode. In order to obviate the error due to loss of carbon dioxide, additional samples of plasma were admitted into the electrode vessel without changing the gas mixture. This was repeated until the tension of carbon dioxide in the vessel was in equilibrium with that in the plasma. Observations were made at room temperature, which was normally 18° C. The reaction of the urine was also estimated by the hydrogen electrode. The reserve alkali of the plasma was found in our first experiments by titrating it electrometrically according to McClendon's technic; but since the more convenient Van Slyke method for the determination of bound carbon dioxide gave results which, for comparative purposes, had a high degree of accuracy, the latter procedure was later exclusively employed.

In considering the experimental results we shall first present the data obtained from the study of blood, then those obtained from the study of urine. Following Sörensen's notation, all hydrogen-ion concentrations are expressed as P_H, the negative exponent of the concentration, C_H. Since $C_H = 10^{-P_H}$, a fall in P_H therefore indicates an increase in hydrogen-ion concentration. The alkaline reserve is expressed in cc. of CO_2 per 100 cc. of plasma.

Results of Observations on the Blood.

Table I consists of representative results obtained from 55 experiments on several dogs and rabbits and a man. In all cases a fall in the bound carbon dioxide occurred after exercise, but no measurable change in the reaction of the plasma was found in any of the 10 instances in which it was determined. The extent to which the alkaline reserve fell after comparable degrees of fatiguing varied with the individual; but in the same subject, under constant conditions of exercise, the percentage drop was essentially the same (Table II).

TABLE I.

Subject.	Weight in kilograms.	Exercise.		Plasma determinations.		
		Distance in miles.	Rate in miles per hour.	Bicarbonate in volumes per cent CO_2.	Percentage fall in bicarbonate.	Hydrogen-ion concentration expressed as P_H.
Dog A	13.2			57.5		7.72
Do		43.7	6.7	47.9	16.7	7.71
Dog C	10.0			53.8		7.65
Do		12.3	8.2	47.9	11.0	7.65
Dog E	10.5			65.3		7.73
Do		20.0	6.1	61.4	6.0	7.73
Man M	61.4			72.9		7.64
Do		10.0	4.0	67.2	7.8	7.65

TABLE II.

Subject: Dog A. Weight: 13.2 kilograms.

Exercise.		Plasma determinations.	
Distance in miles.	Rate in miles per hour.	Bicarbonate in volumes per cent CO_2.	Percentage fall in bicarbonate.
0	0	57.4	0
34.3	7.6	49.8	13.2
0	0	53.7	0
32.2	7.3	46.0	14.3

In seven of the experiments, samples of blood were drawn from the subjects at regular intervals in the course of their exercise. The data thus obtained were of two classes:

1. In the instance of the large dog A, whose maximum muscular performance was at no time demanded, there was a continuous drop in the reserve alkali, varying almost as a linear function of the distance, after a rapid initial fall probably attributable to the changed character of the respiration (Table III). It would have been highly desirable to maintain the rate of exercise constant throughout the experiment but this was impracticable. It is noteworthy that an acceleration of the speed of the treadmill during the last quarter of the 65-mile run, caused the bound carbon dioxide to fall more rapidly. Curve (a) of Figure 1 shows this graphically.

TABLE III.

Subject: Dog A. Weight: 13.2 kilograms.

Exercise.		Plasma bicarbonate in volumes per cent CO_2.
Distance in miles.	Rate during last increment of distance run.	
0	0	54.7
12.5	8.4	46.0
22.9	6.9	46.0
32.1	6.2	44.1
39.9	6.2	42.2
49.6	7.8	41.3
65.5	8.0	37.5

Total distance=65.5 miles.
Average rate=7.5 miles per hour.
Total percentage fall in plasma bicarbonate=31.4.

TABLE IV.

Subject: Dog C. Weight: 10 kilograms.

Exercise.		Plasma bicarbonate in volumes per cent CO_2.
Distance in miles.	Rate during last increment of distance run.	
0	0	59.6
1.3	7.7	58.2
7.2	7.0	54.9
14.0	7.5	53.9
20.0	6.2	53.9
23.3	3.4	53.9
26.9	3.9	53.9
30.7	3.6	53.9
34.4	4.3	53.9
37.3	3.7	53.9

2. In the instance of smaller dogs, as C, whose capacity for muscular activity was quickly reached by the available speed of the treadmill, the reserve alkali dropped gradually to a point below which it did not fall (Table IV). Then as the dog was unable to run longer at a high rate, the speed of the treadmill was decreased to less than 4 miles per hour. Although he continued to run for a total distance of 37.3 miles, there was no further change in the bicarbonate content of his plasma. This would suggest that a condition of equilibrium obtained in the organism. Curve (b), figure 1, illustrates the difference between this and the above experiment.

The relation between the rate at which the reserve alkali returned to its original concentration and the amount of exercise is shown in Table V. The bicarbonate of a small dog G fell rapidly when he was forced to run a short distance at high speed. The recovery was complete, however, at the end of one hour of rest. In another instance, when the distance run was relatively greater, the recovery amounted to only 37 per cent of the total fall after two hours of rest. This might be interpreted as pointing to an accumulation of fatigue substances in the organism.

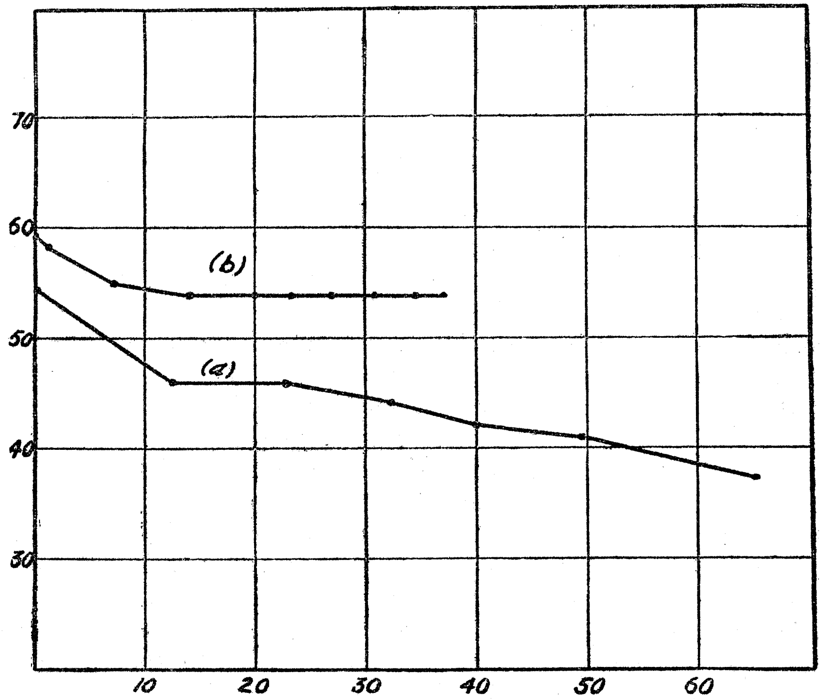

FIG. 1. Graphs representing the change of plasma bicarbonate in (a) a large dog, fatigued at a high rate of exercise, long maintained; and in (b) a small dog, fatigued at a high initial rate which was subsequently decreased. Distance is plotted along the axis of the abscissas in miles. The bound carbon dioxide is plotted along the axis of the ordinates in volumes per cent of CO_2.

TABLE V.

Experiment 1.—Subject: Dog G.

Exercise.		Plasma bicarbonate in volumes per cent CO_2.
Distance in miles.	Rate in miles per hour.	
0 1.3	0 7.8	59.5 44.8
After one hour of rest=		59.5

Experiment 2.—Subject: Dog G.

Exercise.		Plasma bicarbonate in volumes per cent CO_2.
Distance in miles.	Rate in miles per hour.	
0	0	61.4
20.0	7.8	46.2
After two hours of rest=		51.9

Percentage recovery in experiment 1=100.
Percentage recovery in experiment 2= 37.

Results of Observations on the Urine.

Because it is fully appreciated that P_H determinations of the urine become significant only when examined with full knowledge of the food ingested by the subject, the following observations are reported with some hesitation on the part of the writer. In the case of the hospital patients it was possible to note the character and amount of the food eaten. It was obviously impossible to do this when studying a large number of factory employees. In order to approach conformity of experimental conditions as nearly as possible, therefore, the P_H results of only those patients who were on a diet similar to that of the average individual were considered as controls. The importance of this is illustrated by the fact that the P_H of the urine of men on "liquids" exceeded by an average amount of 0.4 the P_H of the urine of men on the "normal" diet.

In Table VI a comparison of the urinary reaction of men at work and at rest is made. The ratio of the final P_H to the initial P_H indicates the direction of the change in the reaction of the urine—a value less than unity denoting increased acidity, one greater than unity, decreased acidity.

TABLE VI.—*Summary of P_H determinations on urine.*

Subjects.	Number of subjects.	Number of observations.	Average P_H of morning urine.	Average P_H of afternoon urine.	Ratio of final to initial P_H.
At rest.............	6	28	5.78	5.95	1.03
At work............	40	289	5.77	5.68	0.98

In the case of the control experiments, the average of 28 observations showed that there was a tendency for the reaction of the afternoon specimens of urine to be slightly less acid than those of the forenoon. Of the 289 observations on 40 factory workers, representing 6 different operations, summarized in Table VI, 67.5 per cent showed a greater concentration of hydrogen-ions at the close of the day's work than at its beginning. This tendency is indicated by the lowered average P_H.

In the course of our study of the urine of factory operatives, a series of observations extending over a period of 2 weeks was made on 12 workers in the foundry. Although these men varied in physical strength, as indicated by the Martin spring balance method, they all completed the same number of "cores" during the working shift. The results of these observations were graphically expressed as follows:

The ratio of the P_H of the afternoon urine to that of the forenoon urine was plotted from day to day for each individual. These graphs were then arranged according to the physical strength of the subject—that of the weakest being at the left, that of the strongest at the right. From this chart it was apparent that:

1. The ratios of those subjects who were physically weak showed wide deviations, both negatively and positively, from the base line. This indicated that the concentration of hydrogen-ions of the urine at times decreased and at other times increased after work.
2. The ratios of the physically strong men, however, not only did not exhibit these irregularities, but lay almost without exception above the base line, thus indicating an increased acidity of the urine following work. This observation may be related to the difference in results obtained when studying the effect of fatigue on trained and untrained men.

The urine of the men who participated in the 12-mile Marathon race was, without exception, of a higher degree of acidity after the run than before (Table VII). No reason is known for the high P_H of the urine before the race. It may be significant that these men had been on a special training diet and had eaten luncheon two hours before the race began. The "alkaline tide" may therefore have been an influencing factor.

TABLE VII.—*Marathon runners.*

Number of subject.	P_H of urine before race.	P_H of urine after race.	Ratio of final P_H to initial P_H.
1	6.32	5.64	0.89
2	7.03	6.84	.97
3	6.27	5.12	.82
4	7.62	5.59	.73
5	7.08	5.03	.71
6	7.67	6.94	.90

The results obtained from two men entered in the bicycle race are of interest, because of the difference between the conditions under which they competed (Table VIII). Bd rode frantically toward the close of the week in an attempt to recover distance lost through penalties, but no such extraordinary efforts were required from Bk, who was not thus handicapped. The urine of Bk remained at a practically constant P_H throughout the week, but the urine of Bd became markedly acid on the afternoon of the fourth day and continued so on the fifth, after which he was forced to withdraw from the race, on account of exhaustion. The diets of these men were unaltered during the week.

TABLE VIII.—*Bicycle riders: Bd, Bk.*

Day of race.	P_H of urine of Bk.		P_H of urine of Bd.	
	10 a. m.	10 p. m.	10 a. m.	10 p. m.
1	....	6.03	5.89	5.75
2	6.10	6.02	5.80	5.65
3	6.24	6.02	5.94	5.91
4	6.17	6.06	6.26	5.36
5	6.04	5.92	5.30	....

The urine of M, whose blood was found to have a lowered bicarbonate content after a 10-mile walk, had a P_H of 4.90 after the exercise as contrasted with a urinary reaction before the exercise of 6.90.

Aducco's observations that the urine of a dog became less acid and even alkaline during exercise were confirmed. Attempts to adjust conditions which would bring about comparable changes in the urinary reaction of men have thus far met with failure. This point requires further investigation.

Summary of Results.

1. Exercise produced a diminution of the bound carbon dioxide of the blood plasma. The depletion, however, did not progress to such a point that the reaction of the plasma was significantly altered.
2. The lowering of the bound carbon dioxide was a function of the rate and the amount of exercise.
3. The rate at which the bound carbon dioxide returned to its original value was related to the amount of exercise.
4. The urine of men engaged in manual labor tended to be of a slightly higher degree of acidity than that of men at rest. This statement could only be made of the class as a whole, and could not be reliably applied to individuals without accurate knowledge of their diets.
5. The urine of physically strong men was regularly slightly more acid after work than before; the urine of physically weak men showed wide variations in its reactions from day to day.
6. When the muscular activity was such that the subject was intensely fatigued, there was invariably an increase in the hydrogen-ion concentration of the urine.

The experimental work was conducted, for the most part, in the laboratory of the department of physiology of Columbia University under the direction of Prof. Frederic S. Lee. The electrometric measurements were made at the Harriman Research Laboratory through the courtesy of Dr. K. G. Falk and Dr. E. J. Cohen.

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THE NOTIFIABLE DISEASES.

PREVALENCE DURING 1918 IN CITIES OF OVER 100,000.[1]

ANTHRAX, CEREBROSPINAL MENINGITIS, DIPHTHERIA, GONORRHEA, INFLUENZA, MALARIA, MEASLES, PELLAGRA, PNEUMONIA (ALL FORMS), POLIOMYELITIS, RABIES IN MAN, RABIES IN ANIMALS, SCARLET FEVER, SMALLPOX, SYPHILIS, TUBERCULOSIS (PULMONARY AND ALL FORMS), AND TYPHOID FEVER—CASES AND DEATHS REPORTED AND INDICATED FATALITIES PER 100 CASES, 1918; AVERAGE NUMBER OF CASES REPORTED DURING RECENT YEARS (1913 TO 1917).

The following tables include data for all cities of the United States having an estimated population of 100,000 or over. Estimates of population in cities were not made by the Census Bureau as of July 1, 1918, and, therefore, case and death rates were not computed.

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[1] It will be noted that some of the cities are apparently much more successful in obtaining reports of the notifiable diseases than are others. This may be due to the greater activity of their health departments or to a greater interest in the public welfare on the part of their practicing physicians. That the health departments of certain cities are securing fairly complete information of the prevalence of preventable diseases is indicated in a number of instances by the large number of cases reported as compared with the numbers of deaths registered from the same causes.